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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,011	BERCHTOLD, HARALD	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *15,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *19 September 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-14 and 16-20, drawn to an insulin analog crystal and a process for preparing the crystal, classified in class 530, subclass 303.

   II. Claims 15 and 21, drawn to a use of an insulin analog(s) crystal for a pharmaceutical preparation, classified in class 514, subclass 3.

   III. Claim 22, drawn to a method of treating Type I or II diabetes, classified in class 514, subclass 866.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I is related to Inventions II-III as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the product as claimed can be used in a materially different process of using the product. For example, the insulin analog crystal can be used in various X-ray crystallography studies. Thus the search for Invention I would not necessarily be co-extensive with Inventions II-III as each would require separate non-patent literature and patent literature searches which utilize unique keywords, also different class and sub-class searching would be expected. As such, an undue search burden would be expected of the examiner.

3. Inventions II and III are directed to related because both methods describe use if an insulin analog crystal. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, the process for preparing a pharmaceutical containing an insulin analog crystal and the process of actually using the prepared pharmaceutical in order to treat Type I or II diabetes are completely divergent in their requisite method steps and end points. For instance, the process of preparing the insulin analog crystal requires taking an insulin analog crystal and drying it a pharmaceutically acceptable buffer, whereas the process of using said pharmaceutical to treat Type I or II diabetes requires the administration of said pharmaceutical to a patient in need thereof. Thus the search for Invention II would not necessarily be co-extensive with Inventions III as each would require separate non-patent literature and patent literature searches which utilize unique keywords, also different class and sub-class searching would be expected. As such, an undue search burden would be expected of the examiner.

4. Because these inventions are independent or distinct for the reasons given above and the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Notice of Possible Rejoinder

5. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain

dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

6. During a telephone conversation with Ms. Barbara Kurys (with Examiner Kim) on 12 January 2006 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-14 and 16-20. Affirmation of this election must be made by applicant in replying to this Office action. Claims 15 and 21-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Status of the Claims

7. Claims 1-14 and 16-20 are presently under examination. Claims 15 and 21-22 are withdrawn at this time from further consideration as they are drawn to non-elected subject matter.

Information Disclosure Statement

8. The information disclosure statement (IDS) submitted on 19 September 2005 has been considered by the examiner. See signed and attached PTO-1449's.

Specification

9. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Appropriate correction is required.

10. The disclosure is objected to because of the following informalities: Examples 1-3 clearly reference Hampton Research "Protein Crystallization Screening Kits" as where the crystallization conditions are obtained from. However, there are 16 different protein crystallization screens; the examiner was able to find the conditions of the first two Examples in Crystal Screen solutions 3 and 11; however, no where were the Example 3 conditions located in any of the Hampton Research protein crystal formulations.

Clarification is required.

Claim Objections

11. Claim 8 is objected to because of the following informalities: The claim presents an amino acid sequence which lacks an appropriate sequence identifier(s) (SEQ ID No). Appropriate correction is required.

12. Claim 8 is objected to because of the following informalities: the conjunction "and" needs to be inserted after the line describing B3. Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 2-7 recites the limitation "the His B10 " in reference to insulin analogs. There is insufficient antecedent basis for this limitation in the claim because His B10, while being conserved in wild-type insulin, may not be in insulin analogs.

15. Claims 2-7 recites the limitation "the molecules of the insulin analog" in reference to claim. There is insufficient antecedent basis for this limitation in the claim because claim one merely recites an insulin analog of a certain space group. There is no mention that the insulin dimer will be anything other than just that, a dimer, and thus the the use of the plural molecules suggests a limitation in claim 1 that is not there (for instance, that in the insulin analog crystal, 3 dimers converge crystallographically to form a hexamer which, is an essential element not recited in claim 1).

16. Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are rendered indefinite because while a crystal may be grown in a pharmaceutically acceptable composition, if they are not grown under such conditions, how it is to be expected that the crystal would maintain its crystalline structure. For instance, it is well known in the art that the pharmaceutically acceptable composition of water, will dissolve most protein crystals upon contact. Thus, it is unclear if Applicants truly are claiming an insulin crystal in an acceptable formulation which will retain its crystalline state, or merely claiming a pharmaceutical composition containing insulin analogs.

17. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what exactly the zinc-free, amorphous powder of insulin analogs are actually dissolved in (e.g. water, buffer, a precipitant, etc.).

18. Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear from the recited claim whether the recited pH range is applicable or required of both precipitants.

Claim Rejections - 35 USC § 112 – 1st Paragraph

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1-14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for crystals of human insulin analogs with a lysine at position 3 and a glutamate at position 29, both in the B-chain of human insulin, does not reasonably provide enablement for any other insulin analog crystal (claims 1-14); or a process of preparing an insulin analog crystal (claims 16-20). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a crystal of an insulin analog with various possible substitutions at positions 1, 3 and 27-29 of the B-chain. However, the specification only adequately describes three human insulin analog crystals with a lysine substitution at position B-3 and a glutamate substitution at position B-29; all of which belong to space group R3 with unit cell dimensions A=81.5 Å ± 1 Å and C=33.3 Å ± 1 Å. Nowhere in

the specification is any other type of insulin analog crystal described. Thus, a skilled artisan, in order to achieve the claimed invention, would be required to determine *de novo* crystallization conditions in order to make and/or use the claimed invention. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In order to make the protein crystals encompassed by the scope of the claims, the following must be clear: (a) the preparation and chemical composition of the

molecules to be crystallized and (b) the crystallization conditions, including methods and reagents used. Crystallization experiments must be done in order to determine if a macromolecule will crystallize, and X-ray diffraction experiments must be done in order to determine if the crystalline macromolecule is encompassed by the scope of the claims. Small changes in any of the aforementioned factors can change the unit cell dimensions and/or space group symmetry of a crystal dramatically (Giege *et al.*, 1994); therefore, precise instruction about how to make protein crystals is required so that undue experimentation is not required.

The specification adequately describes how to make a three crystals of human insulin analogs with a lysine at position B3 and a glutamate at position B29, all with R3 space groups which fall within the instant genera of crystals. The protein was crystallized by vapor diffusion using three different precipitant solutions and where the protein solution kept constant at 20 mg/ml and was obtained by dissolving the zinc-free protein in unbuffered distilled water at pH 2.0, adjusted with HCl. Example 1 describes using 0.4M ammonium dihydrogenphophate at pH 4.2, Example 2 describes using 1M ammonium dihyrogenphospate and 0.1M trisodium citrate at pH 5.6 and Example 3 describes using 0.2 ammonium sulfate and 20% PEG 3350 at pH 6.0. Such clear and careful accounting of the crystallization procedure is required and enabled for one of skill in the art to also produce these same insulin analog crystals.

In the instant case, because the scope of the claim exceeds that which is described, the quantity of experimentation would be considerable because the smallest change in any parameter in crystallizing a protein can have enormous consequences.

Thus, it is not enough to have the crystallization conditions of a "native" protein. Rather, what would be required is precise instructions about how to make each and every protein crystal (e.g. conditions for each and every insulin analog protein contemplated for crystallization) in order to avoid undue experimentation. However, there is no direction or guidance in the specification above description of the three insulin analog crystals with a lysine substitution at position B-3 and a glutamate substitution at position B-29 belonging to space group R3, of how a skilled artisan might achieve other insulin analog protein crystals. The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a mutant or a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th

paragraph, lines 1-2). Furthermore, the prior art is of limited assistance because there are no insulin analog proteins which crystallize in the same space group (there is only wild-type insulin). Thus, when all things are considered and the Wands factors are treated on their merits, the claim is not enabled because a great deal of undue experimentation would be expected and necessary in order to practice the claimed invention.

Written Description:

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to crystal analogs of insulin that have a substitution at B1 (present or deleted), B3 (replaced by a basic amino acid) and/or B27-29 (at least one of these replaced by a neutral of acid amino acid) and belonging to the rhombohedral space group R3. While the structure and function of some species of said genera of insulin analog crystals are disclosed in the specification, the common structural characteristics of species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The specification fully describes three crystals of human insulin analogs that fall within the instant genera of crystals. Examples 1-3 describe the crystallization an insulin analog with B1 (phenylalanine) present, B3 has an asparagines to lysine substitution and lysine B29 is substituted by glutamate. All three crystals have the same space group R3 and unit cell dimensions and only differ in the content of the precipitant of the crystallization solution.

While the claim language requires a function for the instant genera of crystals (that of insulin), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately *structurally* described, the following must be adequately disclosed in the claims: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. The three species

noted above have adequately met this burden in the specification. However, the composition of the crystals encompassed by the breadth of the claims is not described. A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Based on the instant specification, the chemical composition, space group, and unit cell dimensions encompassed by the breadth of the claims is unpredictable to one of skill in the art. One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of insulin analog crystals are also not adequately described.

21. Claims 2-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The point at issue is the lack of description of the three-dimensional structural limitations which are present in the claims. For example, the limitation that histidine B10 is present as a hexamer must be assumed to be a result of non-crystallograhic symmetry as insulin in general is present in solution as a dimer (claim 2), the limitations that histidine B10 is coordinated to water (claim 3), dihyrogenphospate ion (claim 4),

monohydrogenphosphate ion (claim 5), a sulfat ion (claim 6) or that the histidines are folded back on onto their own dimer (claim 7) are all mere speculation without presentation of structural information (e.g. atomic coordinates or three-dimensional representations). A skilled artisan could quite easily look at the of the existing prior art such as Whittingham et al. Figure 1, p. 15554 (Biochemistry, 1995, 34: 15553-15563) and deduce that histidine B10 *will* coordinate to some sort of ion, that it *will* form a hexamer where each of the histidine B10 molecules coordinates at least one ion in the center of the 3-fold non-crystallographic symmetry axis (especially assuming an R3 space group), however, whether or not Applicant's structure did so or not is the point at issue. The matter of adequate written description is subject dependent, and in the case of protein crystallography, adequate written description when claiming three-dimensional structural limitations will require actual molecular atomic coordinates, or at the very least three-dimensional drawing representations of the claimed structural features, which leads one of ordinary skill in the art to recognize that the Applicant was in possession of the claimed invention at the time of filing. This of particular importance in this case since there are no insulin three-dimensional crystal structures (wild-type or analogs thereof) that are zinc-free, other than the Wittingham et al. phenol-insulin structure.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly

> conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The issue of a lack of adequate written description may arise (even in original claims) when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ertl et al. (US 6,221,633 B1). Ertl et al. teach insulin derivates where asparagines B3 is replaced by a naturally occurring basic amino acid, and at least one amino acid residue in positions B27, B28 or B29 is replaced by another naturally occurring neutral or acidic amino acid, which is found in a pharmaceutically acceptable composition in either a dissolved, amorphous or crystalline state (claims 1 and 37). As described in Section 15

above, most protein crystals will not retain a true crystal lattice because of the break and damage caused by the "ingredients" of a pharmaceutical composition. It is known in the art the removing a protein crystal from its original crystallizing conditions will almost always destroy the delicate crystal lattice. Thus, Ertl et al. anticipate this claim because the space group R3 would cease to exist.

Reference of Interest – Not Relied Upon

24. Havelund (US 6,818,738) teaches a method for preparing zinc-free crystals of insulin analogues which uses a mixtures of alcohols and salts and a pH of 7.0-9.5.

25. Havelund (US 6,310,038) teaches zinc-free insulin analog crystals which belong to the cubic crystal system.

Conclusion

26. No claim is allowed.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMN
22 February 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER